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EXAMINER	
HAMA, JOANNE	
ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
10/11/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/534,043	SAKAGUCHI, NOBUO	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed, after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *7-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group 1 in the reply filed on August 16, 2007 is acknowledged.

Claims 7-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 16, 2007.

Claims 1-6, 12, drawn to a transgenic non-human mammal comprising a transgene construct comprising a nucleic acid sequence encoding GANP, a cell obtained from said transgenic non-human mammal, and a method of producing a high-affinity antibody using the claimed transgenic non-human mammal.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements (IDS) on May 5, 2005, and May 31, 2006. The references on the May 31, 2006 IDS have been considered.

The reference, CD, Fujiwara et al., 2002, cited on the May 5, 2005 IDS, was not considered, and thus, lined through on the IDS, because while Applicant has provided 3 publications written in Japanese, it could not be determined which (if any) was Fujiwara et al. In addition to this, Fujiwara et al. does not appear to have been cited on the translated search report submitted by Applicant. As such,

the Examiner has no guidance as to the degree of relevance of Fujiwara et al. found by a foreign office. Should Applicant wish to have Fujiwara et al. considered, Applicant must provide a concise explanation (e.g. translation of the abstract) of the relevance of Fujiwara et al.

Drawings

Applicant has submitted a petition that color drawings be accepted in the instant Application, May 5, 2005. See PTO-90C (attached to Office Action) for statement approving entry of color drawings.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

The written description requirement for a claimed genus is satisfied by sufficient description of a representative number of species by actual reduction to

practice and by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant were in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The claims broadly encompass the use of GANP from any species of animal. While the specification teaches that human and mouse GANP were known at the time of filing (specification, pages 5-6, SEQ ID NOs. 1 and 3), the specification does not provide guidance in obtaining GANP sequences from other species of animals. The specification generally indicates that GANP proteins encompassed in the invention include mutant GANP proteins which have deletion, substitution, and/or addition of amino acids and wherein the protein has the same RNA primase activity as that of the wild type GANP protein (specification, page 6). While the specification generally provides these parameters, the parameters do not provide guidance in arriving at GNAP proteins encompassed by the claims. For example, the claims would encompass the use

of the RNA primase from Sulfolobus solfataricus (e.g. see Lao-Sirieix and Bell, 2004, J. Mol. Biol., 344: 1251-1263). The sequence of this protein would fit the criteria of that described in the specification as the protein would be comprised of deletion, substitution, and/or addition of amino acids and has RNA primase activity. While the specification also indicates that other nucleic acid sequences can be obtained by hybridization, and that the nucleic acid encodes protein that has RNA primase activity (specification, page 6, 5th parag), the teaching would pull out proteins that have RNA primase activity (e.g. only the domain having this activity), but not necessarily encode GANP.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing.the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision all the possible variant nucleic acid sequences which would hybridize but do not encode GANP protein, nor can an artisan envision enzymes that have RNA primase activity and are GNAP, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it

is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only full length human and mouse GANP consisting of the recited SEQ ID NOs. 1 and 3 meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-6, 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8

USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

As discussed in the Written Description rejection, the claims encompass the use of a GNAP gene from any species of animal. While the specification provides guidance for mouse and human GANP, the specification does not provide guidance for an artisan to obtain other nucleic acids that encode GANP from other species of animal. With respect to this issue, the claims are limited to mouse and human.

While the goal of the instant invention is to introduce a nucleic acid sequence encoding GANP, the art of transgenesis teaches that that making a transgenic non-human with a phenotype that is predictable is not routine in the art. (In this case, the phenotype is the claimed non-human mammal exhibiting the production of high affinity antibodies to an antigen.) Franz et al., 1997, J.

Mol. Med., 75: 115-129 teach that even when an artisan may take into consideration the genetics and regulation of a candidate gene and the tissue/cell type in which the altered expression is carried out in a transgenic animal, an artisan can still run into limitations and difficulties as unexpected results or no effects in the transgenic phenotype occur. Choice of the animal species and unexpected functions of the candidate gene or compensatory alterations of other genes may contribute to these phenomena. In addition to these problems, Franz et al. also indicate that non-specific effects, such as environment, dietary differences, the genetic background, and positional effects due to the integration of the transgene in overexpression models can modulate the level of gene expression (Franz et al., page 116, 1st col., 3rd parag.). More recent art support the teachings of Franz that an artisan cannot predict the phenotype of a transgenic non-human mammal. The art indicates that there are limitations in using transgenic animals as models of disease. Racay, 2002, Bratisl Lek Listy, 103: 121-126, teaches that:

> "mutations of some genes led to phenotype showing severe defects, which did not correspond to any clinically important disorder, indicating either high *in vivo* stability of the gene or the interspecies differences. From the view of human medicine, the differences among the species (it means the differences in genetic background, gene expression, metabolism, and signal transduction) represent the main limitation of the use of genetically modified animals as models of human diseases. Therefore some results acquired by this approach can not be applied in human medicine because of the differences between rodents and human beings (Racay, page 124, under point 5)."

Jakel et al., 2004, Nature Reviews: Genetics, 5: 136-144 provides examples of transgenic mice wherein species-specific differences between the mouse model and human disease are illustrated. In the case of making a rodent model of ALS, Jakel et al. teach that while the human disease is caused by transmission of one mutant copy of the disease, the phenotype in the rodent model is only observed when the mutant human gene is expressed at high copy numbers in the presence of wild-type rodent SOD-1. Jakel et al. teach that the reason for this difference is not clear, but reflects a species-specific attribute that renders rodents less vulnerable to the mutant human protein (Jakel et al., page 137, 1st col., 2nd parag.). In the case of making a mouse model of Huntington's disease, Jakel et al. teach that part of the difficulty in making a mouse model likely stems from the species differences of mouse and humans. These species differences include a rodent's basal ganglia is less vulnerable that its human counterpart, and that basic cellular biology, such as post-translational modification, is different from humans (Jakel et al., page 137, 2nd col., 3rd parag.). Thus, the art at the time of filing clearly establishes the unpredictability of determining the phenotype of transgenic non-human mammals even when the activity of the gene has been extensively studied *in vitro*, and further establishes the unpredictability of generating a transgenic mouse with a predictable phenotype. It is noted that while Racay and Jakel et al. teach transgenic mice in the context of disease models, the issue at hand is that obtaining transgenic non-human mammals with a particular phenotype are unpredictable. As these issues apply to the instant invention, the specification teaches that a nucleic acid encoding mouse GANP

operably linked to a human Ig enhancer and promoter (specification, page 34) was used to make transgenic mice, the specification does not provide guidance, in light of the above teachings, that mouse GANP expressed in other non-human mammals will also result in non-human mammals that exhibit an increase in high affinity antibodies. In addition to this issue, the art teaches that somatic hypermutation (SHM) is the predominant mechanism in mice and humans, where gene conversion (GC) occurs in chickens and some other species (Li et al., 2004, Genes and Development, 18: 1-11; page 1, 1st col.). As this issue applies to the instant invention, it is unclear whether overexpression of GANP in other species of mammals, other than mice, will result in mutations that occur frequently such that high affinity antibodies can be identified and detected in other transgenic non-human mammals. As such, with regard to these other mammals, it is unclear whether they would be any better at making high affinity antibodies than their wild type counterparts. As such, the specification only provides guidance for an artisan to use mouse GANP in a transgenic mouse.

The claims encompass any transgenic non-human animal made from an ES cell. However, at the time of filing, the art teaches that the only known non-human animal in which embryonic stem (ES) cells can be obtained was for mouse. This is because mice are the only mammals in which ES cells can be generated and which chimerism from ES cells extend to the germline (Murray, et al. (1999, *Transgenic Animals in Agriculture*, CAB International: Oxon, pages 58-61, page 60 2nd parag.). Further, according to Murray, et al., 1999, *Transgenic Animals in Agriculture*, CAB International: Oxon, pages 58-61, the "isolation of

ES cells has not been accomplished unequivocally in other species, including in domestic livestock (Murray, et al., page 59, lines 3-4)." As the teachings of Murray et al. apply to the instant invention, while the art teach how to make transgenic mice with ES cells, neither the specification nor the art teaches how to obtain ES cells from other species of mammals such that an artisan can obtain a line of transgenic non-human mammals comprising the transgene of interest. In addition to this, it is noted that the claims are drawn to a non-human mammal and its progeny. This means that it is required that germline transmission occurs in order to arrive at progeny. In order to obtain the claimed progeny, an artisan is only limited to mouse ES cells. Thus, while the specification and the art teach transgenic mice, the specification and the art do not provide guidance for the full breadth of the claims.

While the specification teaches that the goal of the invention is to use the transgenic non-human mammal comprising a GANP transgene in a method of producing high affinity antibodies (specification, page 7, under "Transgenic Mammal Carrying GANP Gene Transferred Thereinto"), the specification does not provide guidance that the method necessarily results in antibodies that exhibit higher affinity for an epitope. First, with regard to Example 4 teaching the production of high affinity antibodies using GANP transgenic mice, the specification teaches that serum was obtained from mice immunized with NP-CG (nitrophenyl group attached to chicken gamma globulin). The serum was then used in an ELISA to see which serum contained antibody that had a higher affinity for NP. The results were illustrated in Figure 28. The results do not

provide guidance that antibodies with higher affinity for NP were necessarily made as the serum contains a mixture of different antibodies. The results can be interpreted such that the GANP mice produced a large quantity of low affinity antibody. Give this possible interpretation, this is not necessarily indicative that high affinity antibody was produced. In the next assay (Example 4), where spleen cells were fused to myeloma cells to produce hybridomas, the specification teaches that hybridomas made from wild type and GANP transgenic mice were tested in ELISA assays for binding to NP2-BSA following growth in HAT media and HT media. While the specification teaches that 6 hybridomas were obtained from the GANP transgenic mouse and one hybridoma was obtained from the wild type mouse, and the results of the affinity of each antibody made from the hybridomas are shown in Figure 29, the figure does not illustrate that 6 hybridomas were tested (there are only 4 black dots in Figure 29). These results suggest that not all antibodies isolated in the HAT and HT screens are high affinity antibodies. In addition to this, the specification does not indicate the concentrations of antibody that were used in the ELISA. Without guidance of the concentrations of antibody used, the results can be interpreted such that the black dots in Example 29 are the result of high concentrations of low affinity antibody. As such, Example 29 does not provide guidance that high affinity antibody was made.

In addition to this issue, the specification teaches that GANP mice exhibit a higher rate of mutations occurring in the V_H186.2 region than that of wild type mice (Example 2, study starting on page 34 of the specification; see also Figure

10). While the specification provides this teaching, the teaching is not necessarily indicative that high affinity antibodies are being made. While the specification focuses on a particular mutation of V_H186.2 (an amino acid substitution from W to L at position 33), the specification does not provide guidance what effect all other mutations in V_H186.2 have on V_H186.2 binding. Figure 10 shows that in addition to the mutation at position 33, the antibodies from transgenic mice also had amino acid substitutions in other regions of the sequence. These other sequences may render an antibody to have less or no affinity for NP. This is a possibility as the art illustrates that a single amino acid mutations can change a protein's activity to a dominant negative (e.g. Kage et al., 2002, Int. J. Cancer, 97, 626-630 teach that a single amino acid change can make a protein function as a dominant negative; page 628, 1st col., under "Dominant negative effect of a mutatnt BCRP cDNA on drug resistance"). Further, the specification does not teach that other mutations other than W to L at position 33 in V_H186.2 could make an antibody with high affinity. For example, wild type mouse 10 in Figure 10 has a V to H substitution in amino acid 37. It is unclear whether this is a mutation resulted in an antibody with a higher affinity.

While the specification focuses on the substitution of W to L at position 33 of V_H186.2 results in antibodies that have higher affinity for NP, the effects of this particular mutation on V_H186.2 cannot be extrapolated to other V_H regions of antibodies to other antigens. This is because not all V_H regions will have a W at position 33 and nothing in the art of specification indicates that the structure of the V_H region at position 33 is critical for affinity for all other antibodies made to

other epitopes. In addition to this issue, while the art teaches that during somatic hypermutation (SHM), nucleotide substitutions, insertions, and/or deletions occur throughout the rearranged V regions and its immediate flanking sequences, there is a preferential targeting to WRCY (W=A or T, R=A or G, C, Y=T or C) and WA motifs, which are known as hot spots (Li et al., 2004, Genes and Development, 18:1-11; page 1, 2nd col., parag. under "The characteristics of SHM"). In Figure 10, nucleic acid sequences 91-99, which corresponds to amino acids 31-33 of V_H186.2, appears to be one such hot spot (the WRCY motif occurs twice in this region of the nucleic acid sequence). While the hot spot may contribute to the amino acid change at amino acid 33, this is not indicative that other hot spots in other regions of V_H186.2 or in other antibodies that have hot spots would result in amino acid changes that make an antibody have higher affinity. As such, with regard to these issues, the characteristics of the antibody with a higher affinity for NP taught by the specification, page 34, Example 10, cannot be readily extrapolated to other antibodies.

In addition to this issue, the claims are drawn to a transgenic mouse that exhibits no phenotype. This means that the claimed mouse looks like a wild type mouse. Nothing in the art or specification provides any guidance as to how to use a transgenic mouse that exhibits no phenotype.

Thus, for these reasons, the claims are rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claim reads as though serum is obtained from the mouse. As indicated above in the Enablement rejection, serum is a mixture of antibodies and includes antibodies with low affinity for an epitope. The omitted steps are: following immunization, spleen cells from the non-human mammal are fused to myeloma cells to form hybridomas, and each antibody clone from the hybridomas are tested for high affinity binding to the antigen.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

It is noted that while a scope of enablement was written, the instant claims broadly encompass any non-human transgenic mammal carrying a GANP gene transferred thereinto, wherein said mammal has a phenotype or has no phenotype.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuwahara et al., 2000, Blood, 95: 2321-2328 in view of Jaenisch, 1988,

Science, 240: 1468-1474, in view of Maas et al., 1999, The Journal of Immunology, 162: 6526-6533.

Kuwahara et al. teach that germinal center-associated nuclear protein (GANP) co-immunoprecipitates with MCM3 (a protein essential for DNA replication) in B cells. Kuwahara et al. teach that it is curious that GANP, which is upregulated in differentiated cells and arrests the cell cycle, binds to MCM3, a protein essential for the progression of the S phase. Kuwahara et al. teach that one possible explanation for this finding is that a function of GANP is inactivation of MCM3 by means of binding (Kuwahara et al., page 2326, 1st col., 2nd parag. to 2nd col., 1st parag.).

While Kuwahara et al. teach an in vitro study of GANP, Kuwahara et al. do not teach the in vivo role of GANP.

At the time of filing, Jaenisch teaches that a common way of obtaining transgenic mouse is to microinject cloned DNA directly into the pronucleus of a mouse egg. Typically, multiple DNA molecules arranged in a head-to-tail array integrate stably into the host genome (Jaenisch, page 1468, 2nd col., 1st parag. under "Microinjection of DNA into pronucleus"). In addition to injecting cloned DNA into the pronucleus, mouse ES cells can be used. When injected into host blastocysts, ES cell can colonize the embryo and contribute to the germ line of the chimeric animal (Jaenisch, page 1469, 1st col., under "Embryonic stem cells"). Jaenisch teach that when a cellular gene is introduced into the germ line under the control of a heterologous promoter, it is assumed that the phenotype arising in transgenic overexpression animals will reveal not only the pathological

consequences of unregulated or ectopic expression of the transgene, it will also help in the analysis of its normal function in development and differentiation (Jaenisch, page 1471, 1st col., 2nd parag.).

While Jaenisch teach that heterologous promoters are used to express a gene of interest in a cell, Jaenisch does not teach a B-cell specific promoter.

Maas et al. teach that a 6.3 kb genomic fragment with the CD19 promoter containing the critical B cell-specific B cell-specific activator protein/pax-5 site was used to make mice that expressed their transgene of interest in B-cells (Maas et al., page 6528, 1st col., 1st parag. under "Transgenic expression of $hBtk^{WT}$ and $hBtk^{E41K}$ under the control of the CD19 promoter").

All the elements known to make an in vivo system to study the effect of GANP overexpression in B-cells in a transgenic mouse are known in teachings by Kuwahara et al., Jaenisch, and Maas et al.

Thus, it would have been obvious to one having ordinary skill in the art to make a transgenic mouse that overexpresses GANP because Jaenisch teaches that a common use of a transgenic mouse is to study gene function. An artisan would have wanted to study gene function of GANP in B-cells because Kuwahara et al. teach an in vitro study that GANP interacts with MCM3 and Jaenisch teaches that a common method used to understand a function of a gene is to overexpress it in an animal such that an artisan obtains in vivo teachings from the study. In order to obtain transgenic mice that overexpress GANP in B-cells, an artisan would have used the promoter taught by Maas et al.

Maas et al. teach that the promoter has been successfully used in transgenic mice.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Joanne Hama
Art Unit 1632